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From	Mary Harrington for Charles E. Lyon, D.Phil.	Number of Pages	8 (including this page)
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Date	February 28, 2007	Client Number	0492611-0505
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Comments	Applicant:	Chau <i>et al.</i>	Examiner:	Rogers, J.W.
	Serial No.:	10/668,045	Art Unit:	1618
	Filed:	September 22, 2003		
	For:	POLYMER-LINKER-DRUG CONJUGATES FOR TARGETED DRUG DELIVERY		


Dear Examiner Rogers

Per our telephone conference of February 27, 2007, please find the following:

- (1) Re-Submission of Originally Filed Appendix A (2 pp);
- (2) Appendix A (4 pp); and
- (3) Stamped return receipt postcard (1 pg) itemizing Appendix A (4 pp) as one of the documents that was included with the original filing on September 22, 2003.

Please feel free to call if you have any further questions.

With best regards,


Charles E. Lyon, D.Phil.
Reg. No. 56630

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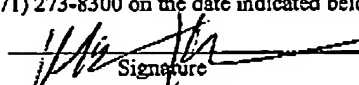
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Chau *et al.*
Serial No.: 10/668,045
Filed: September 22, 2003
For: POLYMER-LINKER-DRUG CONJUGATES FOR TARGETED DRUG
DELIVERY

Examiner: Rogers, J.W.
Art Unit: 1618

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Sir:

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I hereby certify that this correspondence is being facsimile transmitted to the US Patent & Trademark Office (571) 273-8300 on the date indicated below.	
February 28, 2007 Date	 Signature
	Mary Harrington Typed or Printed Name of person signing certificate

RE-SUBMISSION OF ORIGINALLY FILED APPENDIX A

This paper is being filed further to a conversation between the undersigned and Examiner Rogers on February 27, 2007. The Examiner had previously contacted the undersigned on October 31, 2006 to inform him that a copy of Appendix A (referred to on page 16, line 16 of the specification) could not be found in the PTO file for this case.

The undersigned confirmed that Appendix A had been included in the original filing by referring to the stamped return postcard which itemized the originally filed papers, including 4 pages for Appendix A. On October 31, 2006 the undersigned faxed Applicant's file copy of the stamped postcard and Appendix A directly to the Examiner for review. On February 27, 2007, the Examiner contacted the undersigned requesting that the undersigned send the same documents to the general PTO fax number so that they can be entered into the file.

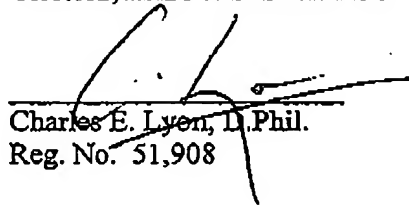
Applicant is hereby complying with this request and respectfully requests that these papers be properly entered into the PTO file. Since Appendix A was present at the time of filing it is Applicant's understanding that a formal Amendment to the Specification is not required in order to add Appendix A to the specification. However, if Applicant is mistaken and a formal Amendment to the Specification is required then Applicant hereby requests that the Specification be amended to include Appendix A. This Amendment would add no new matter since Appendix

A was present at the time of filing as evidence by the stamped return postcard and as acknowledged by the Examiner during the call held on February 27, 2007.

Please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully Submitted,
CHOATE, HALL & STEWART LLP

Date: February 28, 2007


Charles E. Lyon, D.Phil.
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APPENDIX A
A PARTIAL LIST OF TUMOR-ASSOCIATED PROTEASES AND THEIR SUBSTRATE SPECIFICITY

PROTEASE	CLASS	SUBSTRATE SPECIFICITY	COMMENTS	REFERENCES
Prostate specific antigen (PSA)	Serine	HSSKLQ↓ (most selective) SS(Y/F)Y↓S(G/S) (most sensitive)	Chymotrypsin-like substrate specificity. Uniquely expressed by prostate glandular cells. Elevated level in prostate carcinoma. Secreted by PC-82 human prostate tumor model	(Denineade, Lou et al. 1997) (Coombs, Bergstrom et al. 1998)
Human kallikrein 2 (hK2)	Serine	(Q/E)(R/K/H)R↓LXY (cleavage sites in semenogelin I and II) PFR↓	Trypsin-like substrate specificity. Uniquely expressed by prostate glandular cells. Elevated level in prostate carcinoma. Activate PSA and uPA. Cleave fibronectin	(Lovgren, Airas et al. 1999)
Urokinase-type plasminogen activator (uPA)	Serine	KKSPGR↓VVGGSVAAH (sequence of plasminogen) GPR↓ GPK↓	Chymotrypsin family. Overexpressed in a number of epithelial cancers. Involved in tumor-associated fibrolysis, associated with malignancy.	(Suzumiya, Hasui et al. 1988) (de Bruin, Verspaget et al. 1989) (Rijken and Groeneveld 1991) (Ke, Coombs et al. 1997)
Fibroblast activating protein α (FAPα)	Serine	Collagenolytic activity- sequence specificity not determined Dipeptidyl peptidase - AP↓	Cell surface antigen of reactive tumor stromal fibroblasts in epithelial cancers or granulation tissue during wound healing. Degrade ECM. Normal tissues are FAP negative.	(Park, Lenter et al. 1999)

PROTEASE	CLASS	SUBSTRATE SPECIFICITY	COMMENTS	REFERENCES
Meprin α	Metallo (Zn^{++})	RPPGF \downarrow SPFR (sequence of bradykinin)	Expressed normally in intestinal and kidney epithelial cells. Secreted or forms a membrane-bound tetramer with β subunits. Elevated levels of meprin observed in colon carcinoma. Degrade ECM.	(Kohler, Kruse et al. 2000) (Wolz, Harris et al. 1991)
Meprin β	Metallo (Zn^{++})	YEE \downarrow EEI SNFD \downarrow DY WM \downarrow DF	Expressed normally in intestinal and kidney epithelial cells. Forms a membrane-bound tetramer with α subunits. Elevated levels of meprin observed in colon carcinoma. Degrade ECM.	(Chestukhin, Litovchick et al. 1997)
MT1-MMP	Metallo (Zn^{++})	PLP \downarrow L	Membrane bound enzymes involved in the activation of MMP-2. Found in a number of cancer types. Constitutively activated.	(Wocessner and Nagase 2000) (Ohkubo, Miyadera et al. 1999)
Cathepsin B	Cysteine	RR \downarrow FR \downarrow	Lysosomal enzymes normally present intracellularly. Broad substrate selectivity. Secreted or membrane bound for some cancer cells (e.g., Cathepsin B in B16 melanoma and colon carcinoma; Cathepsin L in lung cancer cells). May degrade ECM.	(Corticchiato, Cajot et al. 1992) (Moin, Cao et al. 1998) (Khalfan 1991)
Cathepsin L	Cysteine	FR \downarrow		(Heidtmann, Salge et al. 1993) (Khalfan 1991)

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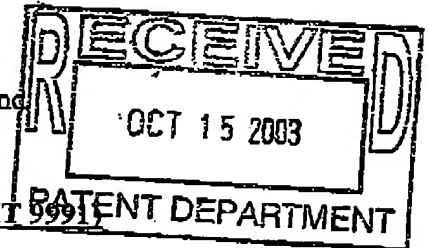
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The Patent and Trademark Office stamping sets forth receipt date (or both the receipt date and the application number) of a Utility Patent Application identified as follows:

Applicant: Chau, et al
For: POLYMER-LINKER-DRUG CONJUGATES FOR
TARGETED DRUG DELIVERY

1. U.S. National Patent Application comprising: 68 pages of specification (including 3 pages of claims, 1 page of abstract and 4 pages of Appendix A) and 25 sheets of drawings;
2. Patent Application Transmittal Letter (4 pages);
3. Statement of Limited Recognition Under 37 C.F.R. §10.9(b) (1 page); and
4. Return Postcard.

Attorney: CEL/izaAttorney Docket No.: 0492611-0505 (MIT 5991)

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